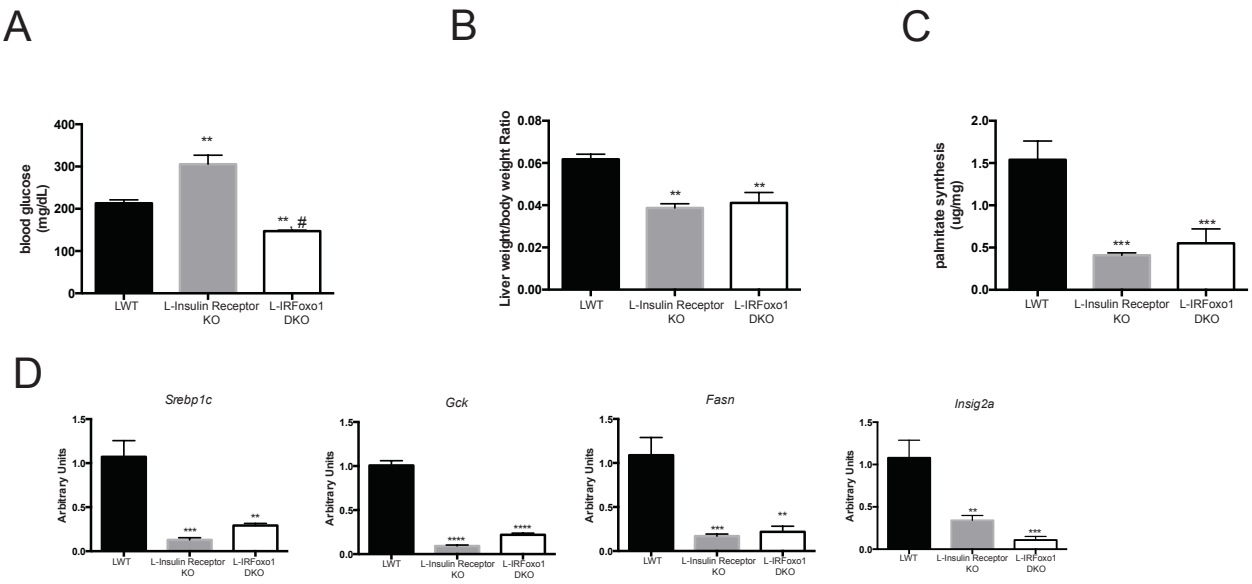
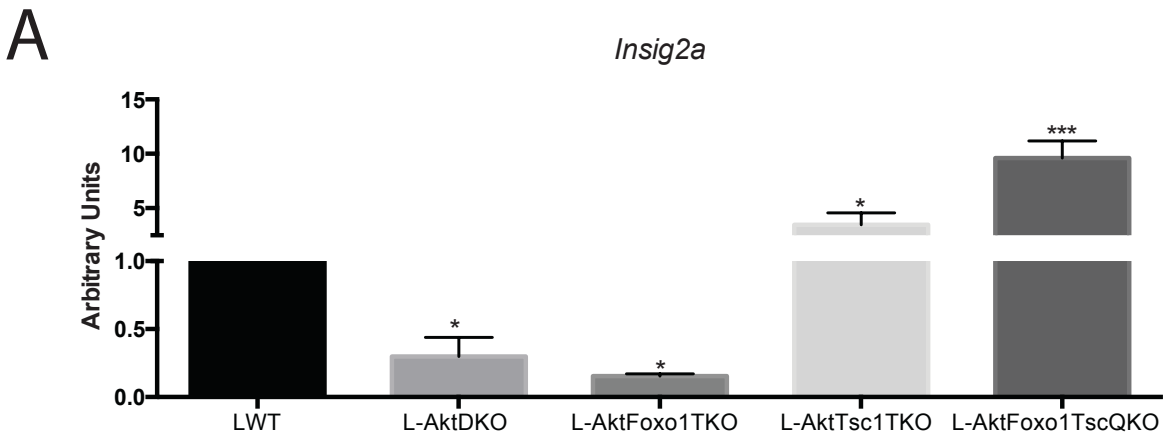
Supplemental Information

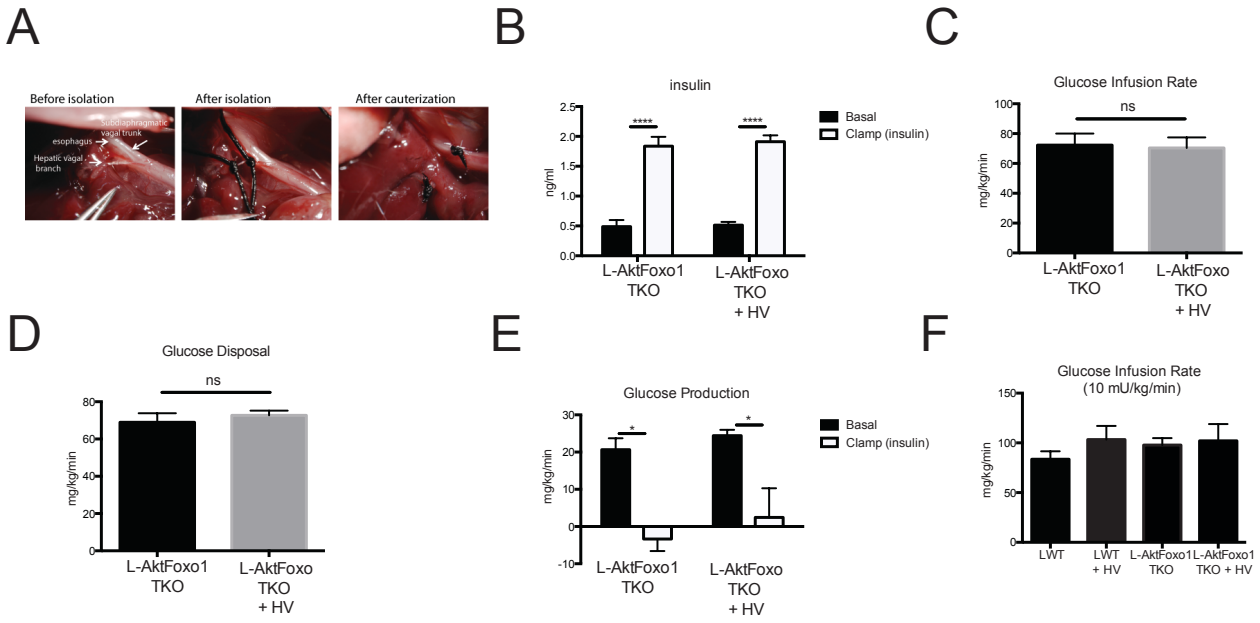


Supplemental Figure 1, Related to Figure 1. Foxo1 deletion does not rescue lipogensis defects in L-Insulin Receptor KO. A) blood glucose following 3 h of feeding after overnight fast **B)** liver weight following 6 h refeeding C**)** *de novo* lipogenesis following 6 h refeeding **D)** gene expression analysis following 6 h refeeding.. n=4 mice/group. **** $p<0.0001$ vs LWT, *** $p<0.001$ vs LWT, ** $p<0.01$ vs LWT , *$p<0.05$ vs LWT. These data are presented as mean ± s.e.m.

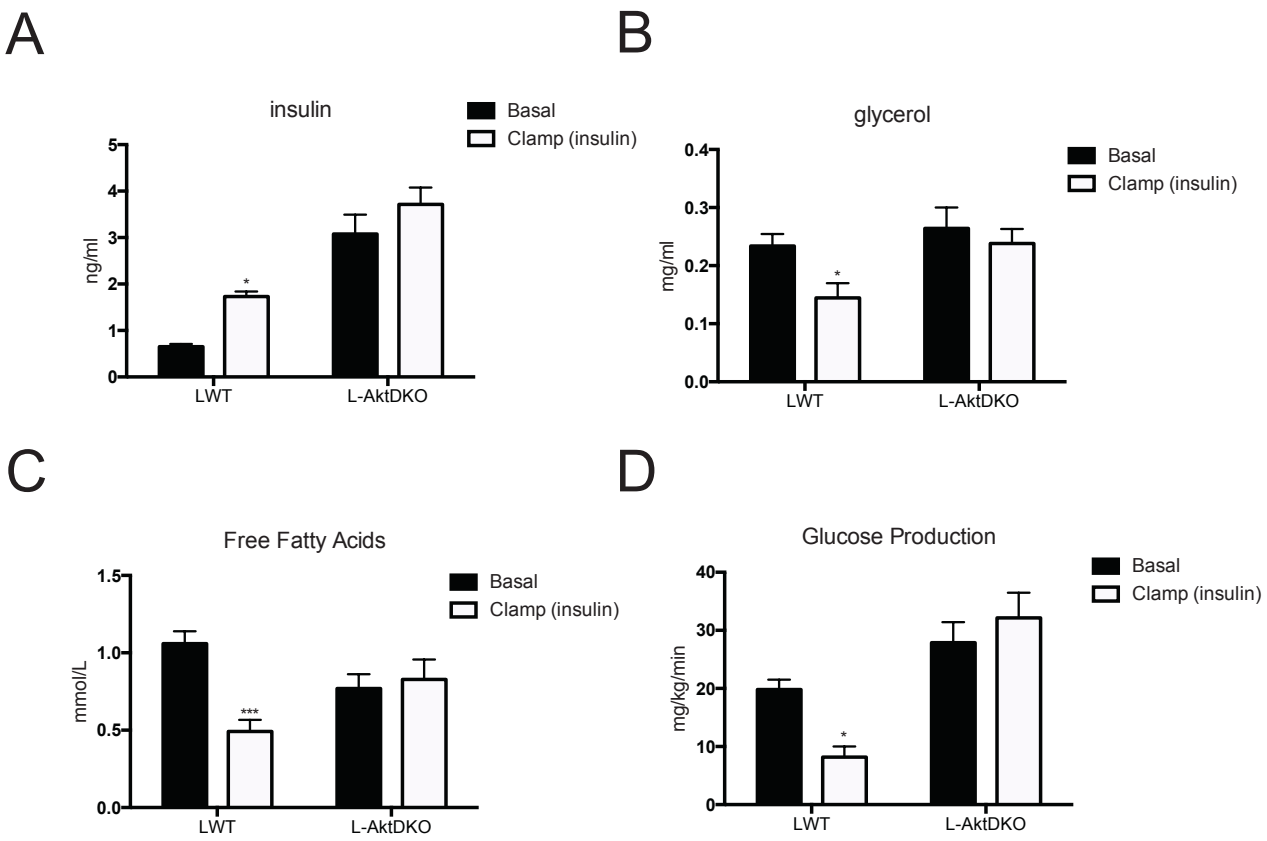


Supplemental Figure 2, Related to Figure 1 and 2. *Insig2a* expression is elevated following *Tsc* deletion independent of hepatic Akt and Foxo1 signaling A) *insig2a* mRNA following 6 h HCD feeding n=3-6 mice/group. *** $p<0.001$ vs LWT, *$p<0.05$ vs LWT . These data are presented as mean ± s.e.m.

Supplemental Figure 3



Supplemental Figure 3, Related to Experimental Procedure "Hepatic Vagotomy". Hepatic vagotomy does not inhibit insulin-dependent suppression of HGP. A) Images of hepatic vagus nerve before and after vagotomy B) Insulin levels during basal and insulin portions of a Hyperinsulinemic-euglycemic clamps using 2.5 mU/kg/min in sham or hepatic vagotomized L-AktFoxo1TKO mice **C)** steady state glucose infusion rate **D)** whole-body glucose disposal (Rd) **E)** hepatic glucose production (HGP) during basal and insulin portions of the clamp n=3 mice/group. **** $p<0.001$ vs sham, * $p<0.05$ vs sham. **F)** steady state glucose infusion rate form hyperinsulinemic-euglycemic clamps performed using a 10 mU/min/kg infusion of insulin. These data are presented as mean ± s.e.m.



Supplemental Figure 4, Related to Figure 5. Insulin does not suppress hepatic glucose production in L-AktDKO mice during hyperinsulinemic-euglycemic clamps due to lack of inhibition of lipolysis. Hyperinsulinemic-euglycemic clamps were performed on unrestrained 5 h fasted LWT and L-AktDKO mice using a 2.5 mU/min/kg infusion of insulin **A)** insulin levels during the basal and clamp period **B)** glycerol levels during the basal and clamp period **C)** free fatty acid levels during the basal and clamp period **D)** hepatic glucose production during the basal and clamp period. n=5-6 mice/group. **p<0.01 vs 20mU * p<0.05. n=5-8. These data are presented as mean ± s.e.m.

Supplemental Table 1. **Serum Biochemical Measurements.**

	LWT	***L-AktDKO***	***L-AktFoxo1TKO***
Fed			
Insulin (ng/ml)	7.11 ± 0.97	22.18 ± 2.4****	19.78 ± 2.08***
Triglycerides (mg/dL)	74.72 ± 6.78	27.86 ± 3.82****	33.4 ± 1.04***
Ketones (mg/mL)	0.10 ± 0.01	0.14 ± 0.02	0.10 ± 0.01

Supplemental Table 1, Related to Figure 1. Serum Chemistry Analysis in Response to High Carbohydrate Refeeding. Serum parameters were measured following overnight fasting and 3 hours of refeeding. **** $p<0.0001$, *** $p<0.001$ n=4-6.

Supplemental Table 2. **Serum Biochemical Measurements.**

	LWT	***L-AktTsc1TKO***	***L-AktTsc1Foxo1QKO***
Fed			
Insulin (ng/ml)	3.51 ± 0.58	6.19 ± 1.4	1.02 ± 0.29**
Triglycerides (mg/dL)	97.86 ± 7.79	62.1 ± 2.9**	145.83 ± 25.20
Ketones (mg/mL)	0.08 ± 0.01	0.15 ± 0.02**	0.09 ± 0.01

Supplemental Table 2, Related to Figure 2. Serum Chemistry Analysis in Response to High Carbohydrate Refeeding. Serum parameters were measured following overnight fasting and 3 hours of refeeding. **** $p<0.0001$, *** $p<0.001$ n=5-6.

Supplemental Table 3. **Serum Biochemical Measurements.**

	LWT	***LWT + PKA-DN***
Fasting		
Triglycerides (mg/dL)	108.25 ± 20.32	145.29 ± 44.28
Free Fatty Acids (mmol/L)	1.80 ± 0.05	2.16 ± 0.16
Ketones (mg/mL)	1.27 ± 0.10	1.81 ± 0.27
Refed		
Triglycerides (mg/dL)	91.14 ± 10.49	99.88 ± 12.71
Free Fatty Acids (mmol/L)	0.82 ± 0.12	0.77 ± 0.09
Ketones (mg/mL)	0.14 ± 0.02	0.15 ± 0.02

Supplemental Table 3, Related to Figure 3. Serum Chemistry Analysis in Response to Normal Chow. Serum parameters were measured following overnight fasting or 4 hours of refeeding normal chow. n=4.